Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A hyaluronic acid-methotrexate conjugate, wherein methotrexate is conjugated with a carboxyl group of hyaluronic acid, a hyaluronic acid derivative, or a salt thereof through a linker containing a peptide chain consisting of 1 to 8 amino acids; or a salt of the conjugate, wherein the linker containing a peptide chain and methotrexate conjugated with the linker is represented by formula (I') or (II'):

$$NH_2$$
 NH_2
 NH_2
 NH_3
 NH_2
 NH_3
 NH_3

wherein R_1 and R_2 are each independently a hydroxy group, an amino group, a C_{1-6} alkoxy group, a C_{1-6} alkylamino group, or a di- C_{1-6} alkylamino group;

L is a linker represented by formula (x):

$$-Q_1-N-Q_2-N-[HA]$$
 R_{11} R_{12}

wherein Q_1 forms, together with -NH- binding thereto, a peptide chain consisting of 1 to 8 amino acids; residues of amino acids contained in the peptide chain are each independently optionally substituted or protected by one or more groups selected from the group consisting of a C_{1-6} alkyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkoxycarbonyl group, a formyl group, a C_{1-6} alkylsulfonyl group, and a C_{6-10} arylsulfonyl group; amide bonds contained in the peptide chain are each independently optionally substituted on the nitrogen atom by one or more C_{1-6} alkyl groups and/or C_{1-6} alkylcarbonyl groups; and carboxyl groups contained in the residues are each independently optionally converted to an amide group optionally substituted by one or two C_{1-6} alkyl groups;

 R_{11} and R_{12} are each independently a hydrogen atom or a C_{1-6} alkyl group;

 Q_2 is C_{2-20} alkylene, wherein the alkylene optionally has 1 to 5 oxygen atoms inserted thereinto and/or is optionally substituted by a carboxyl group or a C_{1-6} alkoxycarbonyl group; and

[HA] represents the position of conjugation with the hyaluronic

acid, derivative, or salt thereof, and the linker forms an amide bond with a carboxyl group contained in the hyaluronic acid, derivative or salt thereof.

- 2. (Cancelled)
- 3. **(Currently Amended)** The hyaluronic acid-methotrexate conjugate or the salt thereof according to claim 1-or 2, wherein the conjugation rate of methotrexate is 0.5% to 4.5% based on the total carboxyl groups of hyaluronic acid.
- 4. **(Previously Presented)** The hyaluronic acid-methotrexate conjugate or the salt thereof according to claim 1, wherein the molecular weight of hyaluronic acid is 600,000 daltons or more.

Claims 5 and 6. (Cancelled)

- 7. (**Previously Presented**) A pharmaceutical composition containing the hyaluronic acid-methotrexate conjugate or the salt thereof according to claim 1 as an active ingredient.
- 8. (**Previously Presented**) A therapeutic drug for joint diseases, containing the hyaluronic acid-methotrexate conjugate or the salt thereof according to claim 1 as an active ingredient.
- 9. **(Original)** The therapeutic drug for joint diseases according to claim 8, which is a topical preparation for administration into the joint.

10. (Previously Presented) A compound of formula (Va) or

(Vb):

[Formula 8]

[Formula 9]

wherein R_1 and R_2 are each independently a hydroxy group, an amino group, a $C_{1\text{-}6}$ alkoxy group, a $C_{1\text{-}6}$ alkylamino group, or a di- $C_{1\text{-}6}$ alkylamino group;

 L_1 is a linker represented by formula (X'):

[Formula 10]

$$-Q_{1}$$
 N $-Q_{2}$ N $-H$ R_{12} $(X ')$

wherein Q_1 forms, together with -NH- binding thereto, a peptide chain consisting of 1 to 8 amino acids; residues of amino acids contained in the peptide chain are each independently optionally substituted or protected by one or more groups selected from the group consisting of a C_{1-6} alkyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkoxycarbonyl group, a formyl group, a C_{1-6} alkylsulfonyl group, and a C_{6-10} arylsulfonyl group; amide bonds contained in the peptide chain are each independently optionally substituted on the nitrogen atom by one or more C_{1-6} alkyl groups and/or C_{1-6} alkylcarbonyl groups; and carboxyl groups contained in the residues are each independently optionally converted to an amide group optionally substituted by one or two C_{1-6} alkyl groups;

 R_{11} and R_{12} are each independently a hydrogen atom or a $C_{1\mbox{-}6}$ alkyl group; and

 Q_2 is a $C_{2\text{--}20}$ alkylene, wherein the alkylene optionally has 1 to 5 oxygen atoms inserted thereinto and/or is optionally substituted by a $C_{1\text{--}6}$

alkoxycarbonyl group.

11. (**Previously Presented**) A process for producing the hyaluronic acid-methotrexate conjugate or the salt thereof according to claim 1, which comprises the steps of reacting the compound of formula (Va) or (Vb) with hyaluronic acid, a hyaluronic acid derivative, or a salt thereof, and converting a carboxyl group of the hyaluronic acid, derivative, or salt thereof to an N-substituted amide group, wherein (Va) and (Vb) are as follows:

[Formula 8]

[Formula 9]

$$NH_2$$
 NH_2
 NH_2
 NH_3
 NH_2
 NH_3
 NH_3
 NH_4
 NH_4
 NH_5
 NH_5
 NH_5
 NH_5
 NH_5
 NH_5
 NH_5
 NH_5
 NH_5
 NH_6
 NH_6

wherein R_1 and R_2 are each independently a hydroxy group, an amino group, a C_{1-6} alkoxy group, a C_{1-6} alkylamino group, or a di- C_{1-6} alkylamino

group;

 L_1 is a linker represented by formula (X'):

[Formula 10]

$$-Q_1 - N - Q_2 - N - H$$
 $R_{11} - R_{12}$
 (X')

wherein Q_1 forms, together with -NH- binding thereto, a peptide chain consisting of 1 to 8 amino acids; residues of amino acids contained in the peptide chain are each independently optionally substituted or protected by one or more groups selected from the group consisting of a C_{1-6} alkyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkoxycarbonyl group, a formyl group, a C_{1-6} alkylsulfonyl group, and a C_{6-10} arylsulfonyl group; amide bonds contained in the peptide chain are each independently optionally substituted on the nitrogen atom by one or more C_{1-6} alkyl groups and/or C_{1-6} alkylcarbonyl groups; and carboxyl groups contained in the residues are each independently optionally converted to an amide group optionally substituted by one or two C_{1-6} alkyl groups;

 $$R_{11}$$ and $$R_{12}$$ are each independently a hydrogen atom or a $$C_{1\mbox{-}6}$$ alkyl group; and

 Q_2 is a $C_{2\text{-}20}$ alkylene, wherein the alkylene optionally has 1 to 5 oxygen atoms inserted thereinto and/or is optionally substituted by a carboxyl group or a $C_{1\text{-}6}$ alkoxycarbonyl group.

12. (Cancelled)

13. (**Previously Presented**) The hyaluronic acid-methotrexate conjugate or the salt thereof according to claim 3, wherein the molecular weight of hyaluronic acid is 600,000 daltons or more.

Claims 14-17. (Cancelled)